What alternatives are there to the use of opioid analgesics in the treatment of chronic pain in light of existing evidence and its limitations?

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Disclosures

Abbott

Sanofi

Bristol Myers Squibb

Allergan

Xenoport

Boehringer-Ingelheim

NUVO

Hind Health Care

Depomed

Alternatives to opioid analgesics

- Drugs most rigorous criteria for efficacy
- Dietary factors not well studied, but potentially important
  - Alpha lipoic acid, acetyl-L-carnitine
- Cognitive-Behavioral Therapy, mindfulness-based tx, educational and group programs
- Exercise regimens
- CAM approaches – many types

Lee and Raja, PAIN 2011; Bell et al, PAIN in press

Alternatives to opioid analgesics

- Device-based Tx (stimulators, pumps)
  - Extremely costly initially and for maintenance
  - Long term efficacy relative to drugs uncertain
- Nerve blocks
  - Little prospectively gathered data on long-term benefit
  - Epidural steroids widely used, even for spinal pain types where benefit has not been demonstrated
  - Costly!
- High strength capsaicin application
  - Effective from 2 weeks onward – substantial initial pain worsening is a risk
  - Administered in office - need to pretreat for procedure pain

Medication Considerations

Selecting the proper medication

- Safety and tolerability in older persons
  - Polypharmacy
- Onset of action
  - Relieve patient's symptoms quickly
- Ease of use
  - Dosing schedule
  - Dosing consistency

Effective Drug Categories

Antidepressants

Anticonvulsants

Topicals

Opioids

Efficacy of Antidepressants

- Tricyclics: highly effective in most pain disorders; also block sodium channels
  - Studies have important limitations
- SSRIs: no efficacy or reduced efficacy
- SNRIs: duloxetine, milnacipran, venlafaxine effective
  - Duloxetine most intensively studied; consistent efficacy in trials

Tricyclic Antidepressants: Adverse Events

- Commonly reported AEs:
  - Blurred vision
  - Cognitive changes
  - Constipation
  - Dry mouth
  - Orthostatic hypotension
  - Sedation
  - Sexual dysfunction
  - Tachycardia
  - Urinary retention
  - WEIGHT GAIN

- Desipramine
- Nortriptyline
- Imipramine
- Doxepin
- Amitriptyline

Caution: all tricyclic antidepressants and venlafaxine have a high fatality rate from overdose compared to SSRIs.

AEs = adverse events.

Mackin GA. *J Hand Ther*. 1997;10:96-109; Beers MH. *Arch Intern Med*. 1997;157:1531-1536; McCue RE. *Clinics in Geriatric Medicine*. 1992;8:323-334; Kapur S et al. *JAMA*. 1992;268:3441-5.

Anticonvulsants: A Large and Diverse Family

Na+ channel blocking

- carbamazepine
- lamotrigine
- oxcarbazepine
- phenytoin
- topiramate
- zonisamide
- lacosamide
- (mexiletine, tocainamide, flecainide)

Other mechanisms

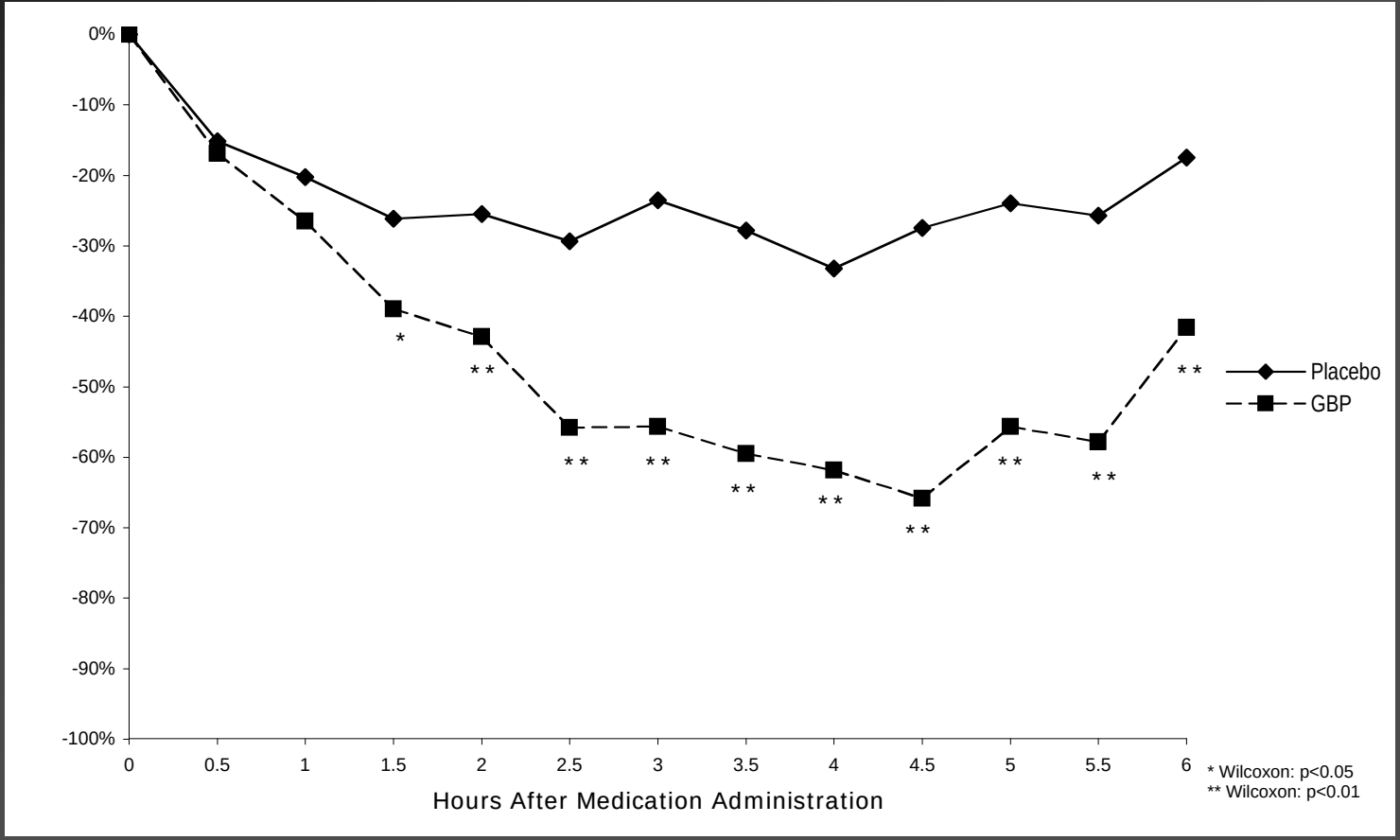
- gabapentin
- pregabalin
- valproate
- clonazepam
- tiagabine
- levetiracetam
- barbiturates

Gabapentin and Pregabalin

- Both FDA approved for pain
- Anticonvulsants: alpha-2-delta subunit on neuronal calcium channels
- Requires active transport system for absorption across intestinal wall - high doses poorly absorbed
- Well tolerated; serious adverse effects rare
  - dizziness and sedation common
  - adjust dose for renal impairment
- No significant drug interactions
- Generic gabapentin available
- Gabapentin prodrug and gastric retention versions

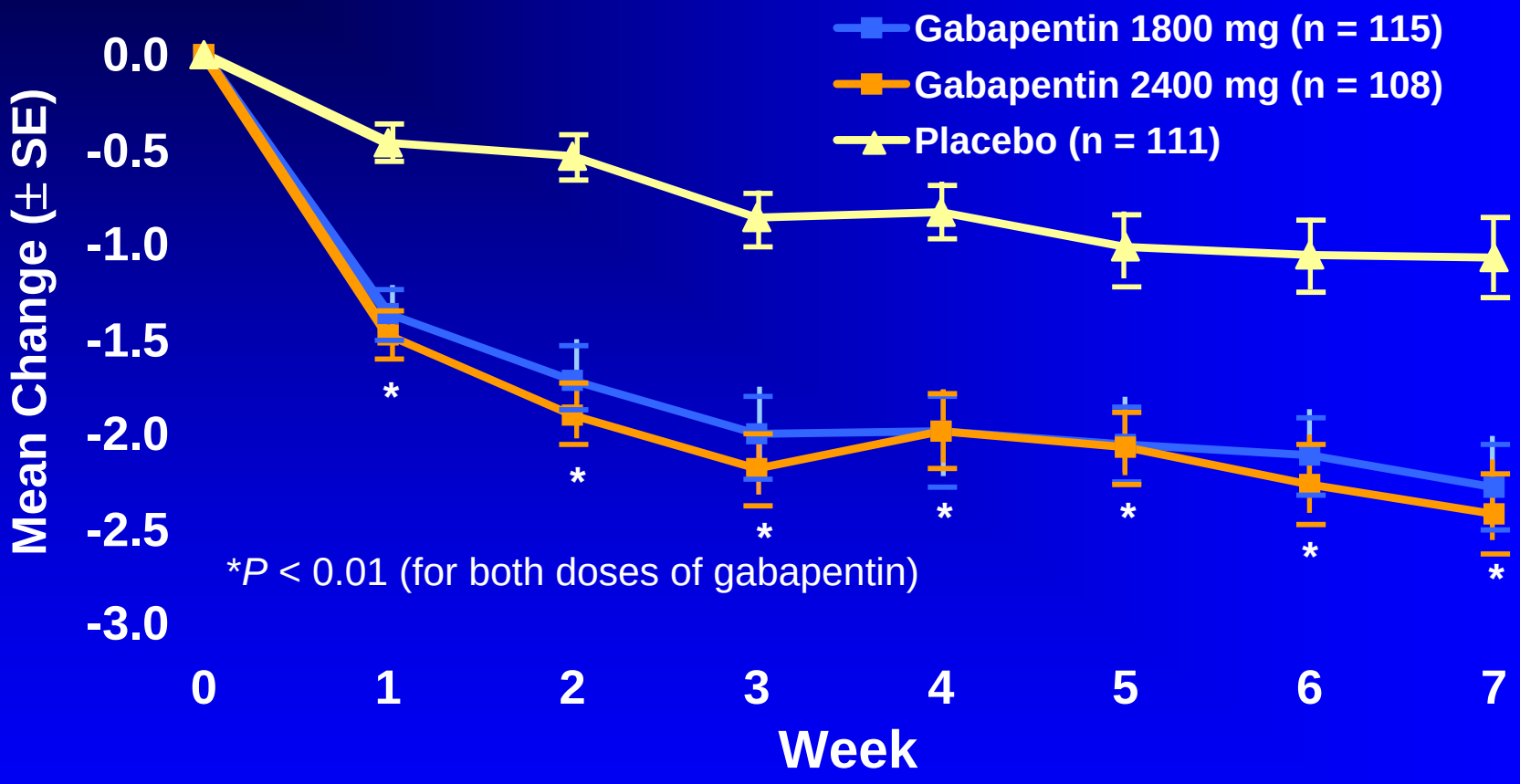
Gabapentin for acute pain

- Effective for acute post-operative pain (>11 published studies)
- Single dose (900 mg) reduces acute zoster pain and allodynia



Berry and Petersen, *Neurology* 2005

Gabapentin in PHN Results (UK): Reduction in Pain Score as Early as 1 Week



Additional benefits of using doses greater than 1800 mg/day were not demonstrated

Rice AS et al. *Pain.* 2001;94:215-224.

Topical vs Transdermal Drug Delivery Systems

Topical (lidocaine patch 5%)

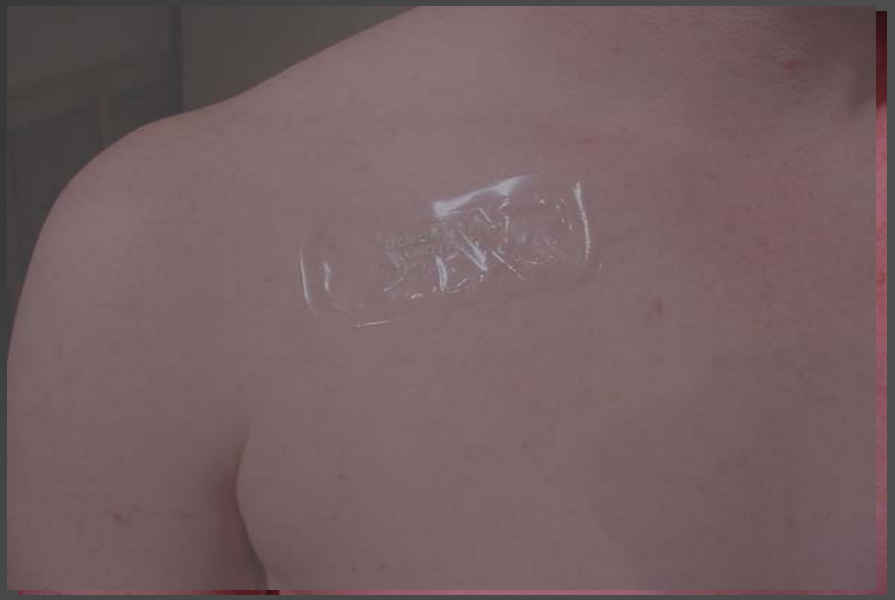
Peripheral tissue activity

Applied directly over painful site

Insignificant serum levels

Systemic side effects unlikely

Transdermal (fentanyl patch)



Systemic activity

Applied away from painful site

Serum levels necessary

Systemic side effects

Topicals

- Lidocaine patch - protective vehicle; low systemic uptake; approved for PHN
- NSAID topicals – several options
- Capsaicin OTC - neurotoxin selectively activates c-nociceptors to produce burning pain (may be severe with initial applications)
- Other drugs and compounded drug combinations available; data anecdotal; unclear if topical or transdermal action
- Benefit outside of neuropathic pain and OA uncertain

Does existing clinical trial data allow a fair comparison of opioids with non-opioids?

- Few studies directly compare the classes by using a crossover design or randomize across classes in a parallel design
  - Raja and Gilron studies important examples, but are small
  - Both indicate opioids more efficacious than a TCA or gabapentin
- Partially enriched enrollment in many opioid trials
- Subject populations may differ
  - Many potential subjects unwilling to try opioids

‘Rational’ Polypharmacy

- Combine approaches with evidence of efficacy in controlled clinical trials
  - Limited number of longer term prospective combination trials
- Avoid unfavorable drug interactions (kinetic/AE)
  - Multiple drugs all producing sedation
- Avoid duplication
- Eliminate ineffective tx before starting new tx
- Therapies for which there is only anecdotal evidence should always be 2nd or 3rd line

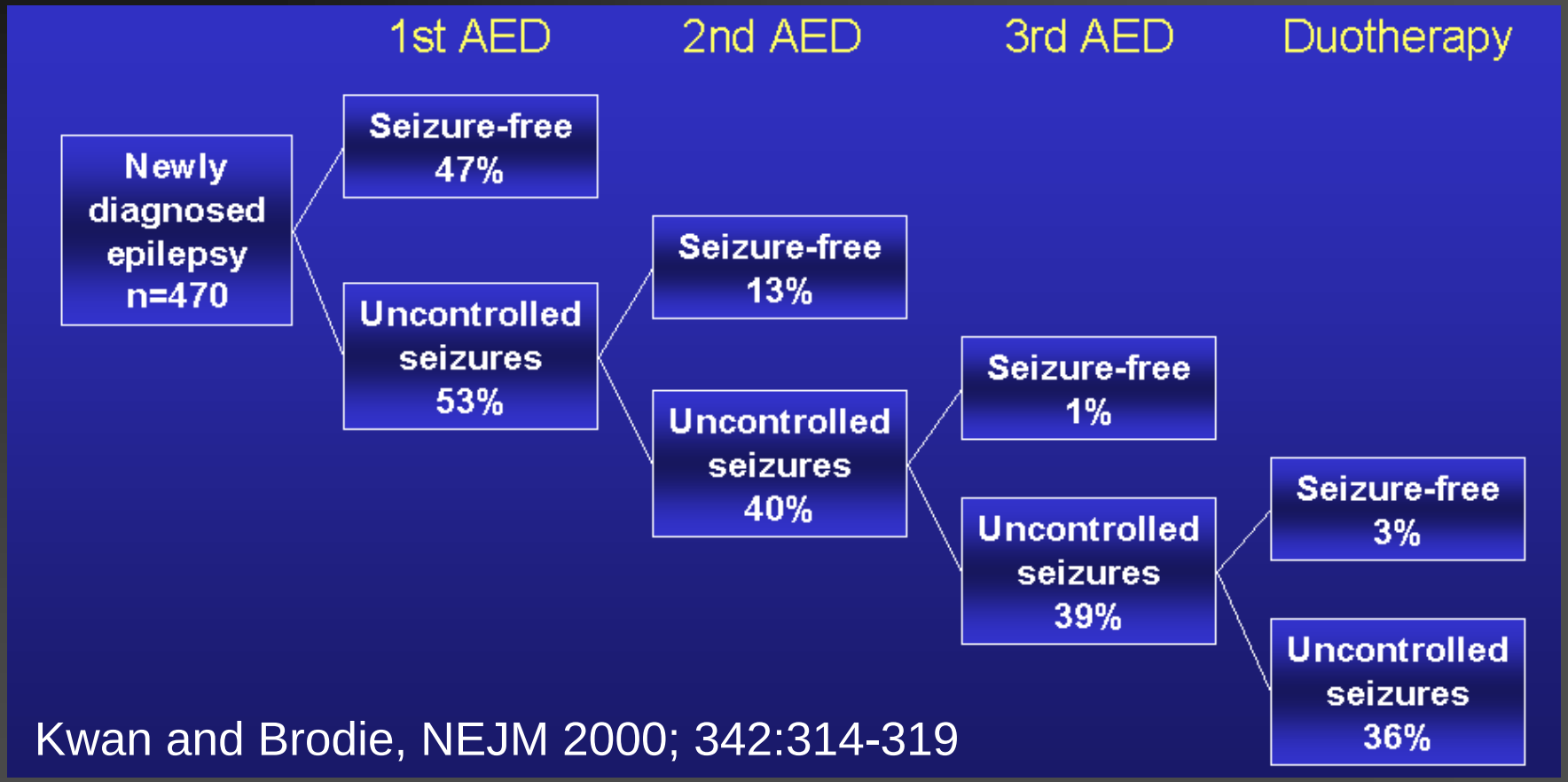
Three Caveats

How representative are the subjects in efficacy trials?

How consistent are the results of trials?

What proportion of the available data is accessible?

Response to sequential treatment trials and duotherapy in epilepsy



Likelihood of success no different if first drug ‘old’ vs ‘new’

Thank you to Ken Laxer

Fifteen Studies of Qutenza were reported to FDA

Protocol #	Phase	Study Design*/Objective	Treatment groups**	Treatment duration	Population^ N		Comments
C101	1	R, DC, OL To determine the relationship between treatment time and loss of cutaneous nociceptors, immunohistochemical changes, etc.	HC LC	30, 60, 120 minutes	HV 20		
C115	1	R, DC, OL To assess the effect of Qutenza on epidermal nerve fiber density and quantitative sensory testing	HC 60	minutes	HV	36	
C102	2	R, DB, DC Efficacy and exploration of anesthesia and analgesia requirements	HC LC	60 minutes	PHN	44	
C107	3	R, DB, DC Efficacy, safety, and tolerability for 3 treatment durations	HC LC	30, 60, 90 minutes	HIV-AN	307	Up to three repeat treatments permitted
C108	2/3	R, DB, DC Efficacy, safety, and tolerability for 3 treatment durations	HC LC	30, 60, 90 minutes	PHN	299	Up to three repeat treatments permitted
C110	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	PHN	155	
C112	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	HIV-AN	5	Terminated early for business reasons
C116	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	PHN	402	Primary support for efficacy
C117	3	R, DB, DC Efficacy, safety, tolerability	HC LC	60 minutes	PHN	418	Primary support for efficacy
C119	3	R, DB, DC Efficacy, safety, tolerability	HC LC	30 or 60 minutes	HIV-AN 494		
C106	2	OL, extension study To obtain information on repeat dosing in patients with PHN	HC	60 minutes	PHN	24	OL extension of C102. Up to three repeat treatments permitted
C109 2		OL Proof of concept study	HC 60	minutes	HIV-AN	12	
C111 2		R, OL To evaluate three local anesthetic formulations used prior to Qutenza	HC	60 or 90 minutes	PHN/DPN 117		All local anesthetics tested were unapproved.
C118 2		OL To assess safety and "efficacy" of repeat treatments of Qutenza	HC	60 minutes (a few patients received a single 90 minute application)	PHN/HIV-AN	106	
C123 N	/A	OL To assess whether a 60-minute Qutenza application was tolerable when used in conjunction with an approved topical local anesthetic [2.5% lidocaine/2.5% prilocaine cream (EMLA)]	HC 60	minutes	PHN	24	

*R = randomized; DC = dose-controlled; OL = open-label; DB = double-blind;
**HC = high concentration (8%, active) patch; LC = low concentration (control) patch
^HV = healthy volunteer; PHN = postherpetic neuralgia; DPN = diabetic peripheral neuropathy; HIV-AN = HIV-associated neuropathy

Snapshot and Scorecard: The RReACT Database 373 analgesic trials posted on ClinicalTrials.gov

Thank you to Kaitlin Greene and Robert Dworkin

- PHN – 93 trials
  - 57 completed
  - 36 have results
  - 23 published in peer-reviewed literature (40%)
- 164 studies DPN
  - 106 completed
  - 72 have results
  - 29 published in peer-reviewed literature (39%)
- 116 studies Fibromyalgia
  - 66 completed
  - 44 have results
  - 29 published in peer-reviewed literature (44%)